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High incidence of brain and other nervous system cancer identified in two mining counties, 2001–2015

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ABSTRACT

Two counties in Montana, Deer Lodge and Silver Bow (DL/SB), have two Superfund sites, as well as an active copper and molybdenum mine in SB. The population living in proximity to these sites are exposed to additional metals and some have been shown to be neurotoxic, especially for children; thus, this study focused on the incidence of brain and other nervous system cancers. The Montana Central Tumor Registry data was used to identify the cases in DL/SB and the remaining 54 counties of Montana (comparison group). After controlling for sex, cancer stage, and year of diagnosis, we found an incidence rate ratio for DL/SB versus comparison group of 6.28 (95% CI: 2.32–17.02) for children ages birth to 4 years, and 3.95 (95% CI: 1.66–9.38) for adults age 30–34 years. The high incidence rate of the brain cancer in the two age groups requires public health action.

1. Introduction

Superfund sites are the nation's most contaminated waste sites, with about 15 million people in the U.S., including about 3.5 million children, living within one mile of a federal Superfund site (Scorecard – The Pollution Information Site, 2011). Metal transport can be on the order of tens of kilometers without change in environmental concentrations (Plathe et al., 2010), so many more people are potentially affected. One of the largest Superfund sites in the U.S. is located in and around Montana's fifth largest city, Butte, in Silver Bow county. Butte is also the home to one of the 12 largest open-pit mines in the US, and in the process of mining for the target metals, other metals are simultaneously extracted. The proximity of the Berkeley Pit, the designated Superfund site, to the active Continental Pit is shown in Fig. 1. These sites are approximately 2 miles apart and both are located in the city limits of Butte. The distance from the center of the Berkeley Pit to the center of Butte is about 2 miles. In addition, the Anaconda Smelting site, also a Superfund designated area, is about 20 miles west of the Berkeley Pit in the neighbouring county of Deer Lodge. The distance from the Anaconda Superfund site to the center of Anaconda is about 3 miles.

Monitoring of Superfund sites is the responsibility of the Environmental Protection Agency (EPA); however, much of their focus is on remediation, and only a subset of the population is typically monitored for toxic exposure through soil sampling and human testing. Local public health authorities with jurisdiction in the exposed areas have traditionally used aggregate data about mortality and morbidity to monitor the human health effects. This study was designed to do a more in-depth analysis of publicly available data from a statewide tumor registry to identify one potential outcome, brain and other nervous system cancers, that is associated with the specific metals identified in the Superfund cleanup and the ongoing mining in the vicinity.

This study compares the brain and other central nervous system cancer incidence experiences of two contiguous Montana counties, Deer Lodge and Silver Bow (DL/SB), to all other counties in Montana. Silver Bow County is home to a large active mining site and the Silver Bow Creek/Butte Area Superfund Site (United States Environmental Protection Agency, 2019a), and Deer Lodge County served as home to the smelter for mining products and the Anaconda Smelter Superfund Site (United States Environmental Protection Agency, 2018). Both sites have had ongoing remediation for the past 36 years, following more than a century of underground copper (Cu) mining that ended in 1982 (United States Environmental Protection Agency, 2019a, 2018; Gammons et al., 2006). Shortly after the closing of the Berkeley pit, Atlantic Richfield opened a new and currently active copper and molybdenum (Mo) open pit mining operation, the Continental pit (United States Environmental Protection Agency, 2019a; Gammons et al., 2006). As a result of exposure to historic wastes and the persistence of open pit mining

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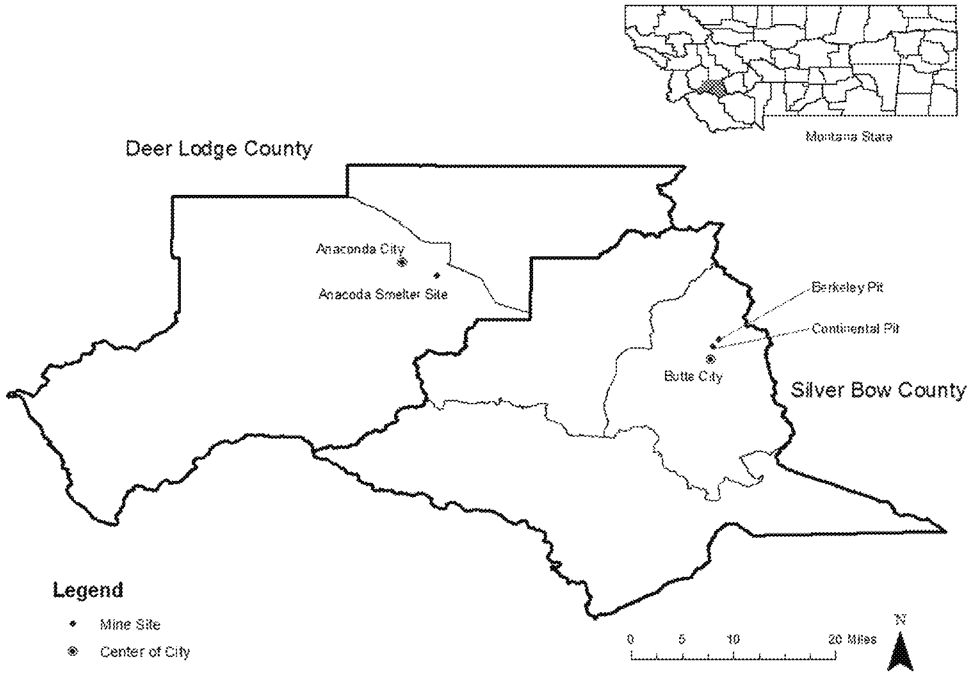

Fig. 1. Locations of Superfund sites and active mine site in Deer Lodge and Silver Bow counties, Montana.
Note: The locations for the center of two cities were based on population distribution.

of Cu and Mo in SB county, arsenic (As), cadmium (Cd), Cu, iron (Fe), lead (Pb), manganese (Mn), Mo, and zinc (Zn) are constantly being released into the atmosphere (United States Environmental Protection Agency, 2019a, 2018; Hailer et al., 2017).

Metals found in these sites have neurotoxic, inflammatory, and carcinogenic properties (Aschner and Costa, 2017); however, the health effects of these exposures have not been adequately studied using epidemiologic methods. Neurotoxic impacts are known to be different when exposure occurs at different ages in humans, so the impact on children can be related to executive brain function, cognition, and behaviour (Hsueh et al., 2017), while in older adults the impact can be chronic conditions such as Parkinson's or Alzheimer's disease (Jaishankar et al., 2014). At all ages, there is potential to develop brain or other central nervous system cancers as a result of chronic exposure to these neurotoxic metals. An important contribution to the literature focuses on the epigenetic alterations in brain tumors associated with heavy metals (Caffo et al., 2014). This study reported the pathway that is impacted by Cd exposure, through differentiation and apoptosis and a resulting loss of expression of tumor suppressor genes and miRNA expression. In addition, data suggest that Pb, As, Cd and other metals cause oxidative stress, cell death, and neuroinflammation, resulting in the formation of radicals in the brain (Mates et al., 2009).

The epidemiologic literature about the association of metal exposures associated with brain and other nervous system cancer is largely limited to occupational exposures to chromium (Cr), Pb and Cd (Schlehofer et al., 2005; Waisberg et al., 2003; Wesseling et al., 2002). Another study found elevated serum concentrations of Cd, Fe, Mg, Mn, Pb, and Zn in patients with malignant glioma tumors compared to controls (Arslan et al., 2011). There are no studies that document the exposures among children with brain or other nervous system cancers. There have been a few studies on health outcomes due to metal exposures for the residents of DL/SB. The 2009 Montana cancer profile reported no significance difference in all sites cancer incidence rates for people of DL/SB (age adjusted incidence rate (IR), cases per 100,000: SB IR = 422.6 (95% CI: 395.3–451.5); for DL IR = 411.6 (95% CI: 363.9–464.7)) when compared to all Montana counties (IR = 438.0 (95% CI: 432.7–443.3)) (US National Cancer Institute, 2009). A recently published study, authored by some members of this study, compared the cause of death in DL/SB compared to the other 54 counties of Montana during the 2000–2015 period. The selected cancers sites, reported in that study, were related to metal exposure, so the calculations reflected cancer of the stomach, liver, pancreas, bronchus and lung, skin, breast, prostate, kidney, bladder and brain. When these sites were combined, the standardized mortality rate (SMR) for cancer was 1.19, 95% CI: 1.10–1.29 (Davis et al., 2019).

This study seeks to characterize the brain and other nervous system cancer incidence experiences of DL/SB residents, who have been historically and currently exposed to hazards from a Superfund site and active open-pit mining. The EPA listed As and Pb the primary contaminants of concern in Butte. There are other contaminates including Aluminum (Al), Cd, Cu, Fe, Hg, Silver (Ag) and Zn (United States Environmental Protection Agency, 2019b). The hypothesis that we tested was that the youngest age group in DL/SB had higher incidence rates for brain and other nervous system cancers compared to their age peers in the other Montana counties. This hypothesis is based on the knowledge that the neurotoxic impact of the metals in the DL/SB environment can result in development of cancer when the brain is developing and maturing.

2. Methods

2.1. Data source and population studied

The study was conducted using Montana Central Tumor Registry (MCTR) data from 2001–2015. The MCTR is supported by Centers for Disease Control and Prevention National Program for Cancer Registries and the Montana State General Fund. Information on the MCTR can be assessed: https://dphhs.mt.gov/publichealth/Cancer/TumorRegistry. The MCTR has a reporting requirement from hospitals, physicians, clinics, and clinical laboratories to provide personally identifying information, tumor/cancer specific data (including stage), and medical procedure information. The study received an exempt review approval, based on the deidentification of the case records, from the University of South Carolina Institutional Review Board in December of 2017.

The study population was restricted to white race, since the number of people from other racial groups was too low (fewer than 10 cases per age group in DL/SB) to report. All cases of brain and other nervous system cancers registered in the MCTR from 2001 to 2015 were used in the numerator. The population years at risk was calculated as the sum of estimated mid-year population from 2001 to 2015 in DL/ SB and remaining counties of Montana, obtained from the United State Census Bureau (United States Census Bureau, 2010). Fig. 1 indicates the location of the two Superfund sites in Butte, Silver Bow County and in Anaconda, Deer Lodge County. The upper right corner of the map also shows the area where cases were identified compared to the remaining area of Montana where the comparison counties are located. In order to determine if the overall brain and other central nervous system cancer rate was elevated, for all ages combined, a nationally representative comparison group was defined from the US Surveillance, Epidemiology, and End Results Program (SEER) data. The SEER 21 Incidence – Crude Rates for Additional Races, 2000–2016 database was used to calculate the standardized incidence ratio (SIR) (National Cancer Institute, 2019 – Surveillance).

3. Covariates

Sex was defined as male or female. Age of diagnosis was grouped in five-year increments, 0–4 years, 5–9 years, ..., 80–84 years, and 85 years and above. Year of diagnosis ranged from 2001 to 2015, grouped into three periods 2001–2005, 2006–2010, and 2011–2015. Four cancer stages were used: localized, regional, distant metastasis, and unknown stage. Brain and other nervous system cancer sites were defined based on the SEER sites as 31,010–31,040.

3.1. Statistical analysis

We had information about age at diagnosis, the sex of the individual, diagnosis year, and cancer stage. We described these variables by frequency (proportion) and mean (SD) for age.

Indirect adjustment, using strata based on age group and sex, was used to obtain standardized incidence ratios (SIRs) and 95% confidence intervals for DL/SB and the remaining counties separately. The number of expected cases was defined by first taking the product of SEER 21 raw incidence rate times person years of observation within a stratum, then summing this product across the strata. SIRs were then calculated by taking the ratio of the number of observed cases to the number of expected cases.

To calculate the incidence rate ratio (IRR), the incidence rate among the exposed portion of the population is divided by the incidence rate in the unexposed portion of the population. This IRR gives a relative measure of the effect of a given exposure and approximates the rate ratio or the odds ratio if the occurrences are rare. Homogeneity of IRR across 5-year age group, sex, diagnosis year group, and cancer stage was evaluated by the Breslow–Day test, separately for each covariate. Stratified analyses were conducted if any inconsistency of IRR was indicated from these tests.

The crude IRR for DL/SB, compared to the remaining counties, was estimated using two-way contingency tables. An adjusted IRR was estimated by fitting a generalized linear model with a log link function. In the model, the log of the probability of developing brain or nervous system cancer for person i was modelled as a function of the covariates, expressed as a vector, x_i.

Thus, $\ln(pi) = x_i\beta$. The exponential of the beta coefficient that corresponds to county of residence is the estimated adjusted IRR. These models control for age, sex, cancer stage, and year of diagnosis, unless stratification by one of these variables is indicated by the Breslow–Day test.

Data management and statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA). The significance level was set at 0.05.

4. Results

The basic characteristics of the individuals who are registered in the Montana Central Tumor Registry during the period 2001–2015 are shown in Table 1. There was no significant difference in the sex (Chi-Square = 0.0171, $p = 0.896$), age ($t = 1.38$, $p = 0.168$), or cancer stage (Fisher's exact $p = 0.119$) between the two groups.

We compared the rates of brain and other nervous system cancers in DL/SB to both the US rates using national SEER data, and to the other counties of Montana. When we used SEER 21 as the reference population, the SIRs for DL/SB and other counties were 1.09 (95% CI: 0.83–1.41) and 1.04 (0.98, 1.10), respectively. Thus, indirect standardized rates were not significantly different when comparing DL/SB and the remaining Montana counties to the US rates.

When comparing the incidence of brain and other nervous system cancers in DL/SB to the remaining 54 counties of Montana, the Breslow-Day test detected heterogeneity of IRR across 5-year age groups. Therefore, IRRs for DL/SB compared to the remaining counties were estimated separately for each age group. The results are shown and plotted in Fig. 2. After adjusting for sex, stage of cancer, and diagnosis year, the incidence rate ratio of brain and other nervous system cancers in DL/SB is 6.28 (95% CI: 2.32–17.02) for the 0–4 year age group, meaning that the risk of new cases of brain and other nervous system cancers is estimated to be more than six times as high in DL/SB compared to other Montana counites, during the study period. Similarly, the IRR in DL/SB is 3.95 (95% CI: 1.66–9.38) for the 30–34 age group. No significant increased rates for brain and other nervous system cancers were found in any other age group included in this study.

5. Discussion

We identified a significant increased rate ratio of cancer in the brain and other nervous system for residents of DL/SB ages 0–4 years (IRR = 6.28) and ages 30–34 years (IRR = 3.95) compared to remaining counties in Montana. It is important to note that although the confidence intervals are wide for the two age groups, the lower ends of the bounds are higher than one, giving us confidence that an elevated risk exists. We identified this statistically significant risk for brain and other nervous system cancer in two age groups because we explored risk in five-year age groups, since there was heterogeneity across age groups when comparing DL/SB to the remaining Montana counties. This finding is important and noteworthy since, when we did not look at age specific rates, there was no significant difference between brain and other nervous system cancer rates compared to both the other counties of Montana and the US SEER population. The age specific elevated rates of these cancers are masked by the overall brain and other nervous system cancer rates. This finding helps us understand why ongoing aggregate cancer surveillance did not identify these high rates.

The hypothesis was supported since the IRR for children birth to age 4 years was statistically significantly elevated. In addition, the IRR for adults ages 30–34 years was also statistically significantly elevated. These findings must be interpreted with the understanding that the number of cases for brain and other nervous system cancer in any age group is small. Brain and other nervous system cancers are the 13th most common type of cancer in Montana and they represent about 2% of all new cancer cases in the state (Montana Department of Public Health and Human Services, 2019). Brain and other nervous system cancers incidence

Table 1
Basic characteristics of individuals with cancers of the brain and other organs of the central nervous system in Montana, 2001–2015.

Characteristics Number of cancer cases	Silver Bow and Deer Lodge $n = 58$	Remaining counties $n = 1076$
Sex (n, %)		
Male	35 (60.3)	640 (59.5)
Female	23 (39.7)	436 (40.5)
Year (n, %)		
2001–2005	20 (34.5)	343 (31.9)
2006–2010	12 (20.7)	346 (32.2)
2011–2015	26 (44.8)	387 (36.0)
Cancer stage (n, %)		
Localized	42 (72.4)	872 (81.0)
Other[a]	16 (27.6)	204 (19.0)
Age (mean, SD)	52 (24)	56 (21)
Summed person-years of observation	615,573	12,513,207

[a] Cases of regional, distant metastasis, and unknown stage were combined.

Age (Years)	Observed Cases[a]	Unadjusted IRR (95%CI)	Adjusted IRR (95%CI)
0-4	5	6.33 (2.34 , 17.16)	6.28 (2.32 , 17.02)
5-9	< 5	1.76 (0.42 , 7.43)	1.74 (0.41 , 7.34)
10-14	0		
15-19	0		
20-24	0		
25-29	< 5	0.67 (0.09 , 4.85)	0.65 (0.09 , 4.72)
30-34	6	3.90 (1.64 , 9.28)	3.95 (1.66 , 9.38)
35-39	< 5	0.91 (0.12 , 6.74)	0.90 (0.12 , 6.70)
40-44	0		
45-49	6	1.83 (0.79 , 4.23)	1.81 (0.79 , 4.18)
50-54	5	0.98 (0.40 , 2.40)	0.97 (0.40 , 2.38)
55-59	7	1.31 (0.61 , 2.82)	1.31 (0.61 , 2.81)
60-64	7	1.25 (0.58 , 2.67)	1.24 (0.58 , 2.66)
65-69	0		
70-74	8	1.29 (0.63 , 2.65)	1.31 (0.64 , 2.68)
75-79	6	1.29 (0.56 , 2.96)	1.30 (0.57 , 2.98)
80-84	< 5	0.51 (0.12 , 2.08)	0.51 (0.12 , 2.07)
85+	< 5	0.73 (0.18 , 3.03)	0.77 (0.19 , 3.17)

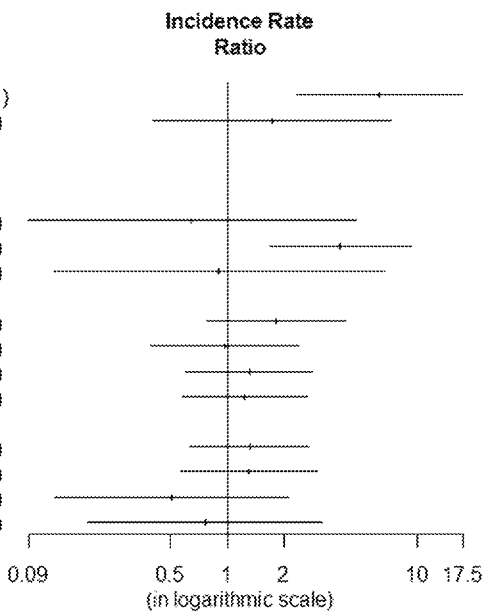

Fig. 2. Age-specific unadjusted and adjusted incidence rate ratios.
Age specific unadjusted incidence rate ratios (IRRs), adjusted IRRs and their 95% confidence intervals (CIs) are shown on left. Adjusted IRRs with 95% CIs are plotted on right. a: Due to the data suppression rules, counts 1–4 are reported as <5 in observed cases.

for residents of DL/SB ages 0–4 years is 1.54 in 10,000 person years compared to 0.24 in 10,000 person years in the remaining counties. Similarly, incidence of brain and other nervous system cancer for residents of SB/DL aged 30–34 years is 1.84 in 10,000 person years compared to 0.47 in 10,000 person years in the remaining counties. However, the risk of brain and other nervous system cancers in very young children and adults in their prime is elevated at a level to cause concern for the residents of these two contiguous counties.

Increased risk for brain and other nervous system cancers was found in adults ages 30–34 years, who were born in the period before the Superfund sites were first declared (1981–1985). However, without a residential history, we do not know how many of these young adults continuously lived in the DL/SB area. Further research is needed to explore associations between metal exposures and brain and other nervous system cancers, that includes residential history, exposure to radiation, family history of conditions associated with brain and nervous system cancer, and other known risk factors. If address history data were available, a geospatial–temporal model could be fitted to quantify the relationship between location of the Superfund and active mining sites and the cases of brain cancer, while considering for correlation across spatial locations and time; and to assess the change of cancer risk and effectiveness of remediation over time. In addition, if sample sizes are sufficient, there is a need for analyses of incidence rates for subtypes of brain and nervous system cancers, and to ascertain biomarkers for metal exposures. Considering the long history of mining, continued open pit mining, and known exposure to toxic heavy metals (Hailer et al., 2017), cancer of the brain and nervous system should continue to be studied and monitored.

Previous studies investigating the association between heavy metal exposure and brain cancers have produced mixed results (Becker et al., 1985; van Wijngaarden and Dosemeci 2006; Anttila et al., 1996; Samkange-Zeeb et al., 2010; Rajaraman et al., 2006; Bhatti et al., 2009; Lam et al., 2007; Cocco et al., 1998; Hara et al., 2010; Schlehofer et al., 2005; Wesseling et al., 2002). However, most of these studies focused on occupational exposures to metals and not chronic residential exposure to contaminated soil, water, or air. The prevailing winds in SB county are southward with the location of the mine north of a large residential neighbourhood (Western Regional Climate Center, 2019). Thus, the potential for inhalation of metals as well as skin absorption, and hand-to-mouth transmission from both water and soil is ongoing (Hailer et al., 2017). Without extensive chemical analyses it is impossible to separate the exposures that are from the residue of old mining that is receiving remediation, from the exposures caused from the active mining that continues in the SB county. The MCTR does not collect information about residential history or individual exposure data, nonetheless, the risk for higher incidence of diseases associated with metal exposure to the residents of the two past and present mining counties is substantial, and the risk needs to be communicated to the population.

The Environmental Protection Agency (EPA) lists contaminants of concern in SB/DL: As, Cd, Cu, Fe, Pb, Mn, Hg, Ag, and Zn (United States Environmental Protection Agency, 2019a), but the only systematic testing that has been conducted in SB/DL is for As and Pb. There is no screening for Mn, Cu, and Zn, although their neurotoxic effects are documented in studies outside the US with impacts as extreme as fetal death and stillborn to intellectual and developmental delay in young children (Reyes et al., 2013; Jomova et al., 2011; Jomova and Valko 2011; Simonsen et al., 2012; Tseng 2004; Bhattacharyya 2009; Shinkai and Kaji 2012; Turker et al., 2013; Caserta et al., 2011).

The research on the epigenetic alterations in brain tumors associated with heavy metals (Jaishankar et al., 2014) suggests the pathway that is altered by cadmium (Cd) exposure, through differentiation and apoptosis, can result in loss of expression of tumor suppressor genes and miRNA expression. In addition, data suggest that Pb, As, Cd and other metals cause oxidative stress, cell death and neuroinflammation, resulting in the formation of radicals in the brain (Mates et al., 2009). The adult brain is thought to be protected from toxins by the blood brain barrier and choroid plexus, nonetheless some heavy metals are able to mimic the behaviour of essential nutrients to be transported to the brain (Bridges and Zalups, 2005). Moreover, toxic metals are capable of producing additive, synergistic, or antagonistic interactions, generating variable biochemical changes in the brain or even reducing the essential micronutrients available (Goyer, 1997). Fetal exposure to metals can happen through the amniotic fluid, the placenta, and the umbilical cord; literature has demonstrated the susceptibility of placental barrier to various toxic substances (Zheng et al., 2014). In a similar manner to the mechanism by which metals cross the blood brain barrier, they are also capable of 'tricking' transport proteins in the cell membranes of the placenta, allowing passage of toxic metals.

While metals induce different toxic effects at different concentrations in the adult, they can also affect important biochemical changes during development. Nuttall (2017) posits two main ways that metals can affect the fetal micronutrient homeostasis. Toxic metals affect the availability of essential heavy metals through competitive chemical bonding (e.g., Pb, Cd can reduce the Zn binding to proteins), and they also can cause secondary micronutrient deficiencies via immune response (Lam et al., 2007). Many metals are known to induce an acute inflammatory response, which in turn can affect essential micronutrient availability. Induction of an acute-phase response during pregnancy can disrupt fetal micronutrient availability, due to rapid changes in protein production and micronutrient metabolism. A comprehensive review of metal mixtures and neurodevelopmental outcomes provides evidence of synergistic effects related to exposures to mixtures of As-Cd-Pb and Mn in the presence of As, Cd, or Pb (von Stackelberg et al., 2015). Their review focused on nonspecific developmental outcomes in children but did not report on brain and other nervous system cancer.

6. Conclusion

This study uses an epidemiologic approach combined with statistical methods that uncover the association of residence in DL/SB counties with extremely high risk for brain and other nervous system cancers in young children, 0–4 years, and adult ages 30–34 years. The approach used to conduct these analyses allowed for heterogeneity by age, sex, year, and stage in which the cancer was diagnosed. We found that IRRs varied by age, but not by sex, year of diagnosis (during our study period 2001–2015), or cancer stages. These findings are important since they have previously been understudied and therefore not reported. The implications are substantial for residents of DL/SB, and also for the millions of Americans who live near a Superfund designated area or active mining sites that contain mixtures of neurotoxic metals.

Declaration of Competing Interest

None.

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